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Efficacy and tolerability of topiramate in childhood and adolescent epilepsy: a clinical experience

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A 3-year retrospective review was undertaken of the use of topiramate in 51 children aged 3–16 years with partial and generalized epilepsies who attended a tertiary referral epilepsy centre in a large children's hospital. The mean follow-up period was 19 months (range 6–33 months). Twenty-six children (51%) were still receiving topiramate at the time of their last review.

Fifteen children (29%) showed a greater than 50% reduction in their seizure frequency and four children (8%) became seizure free, three on topiramate monotherapy. The drug appeared to be most effective in children with moderate learning difficulties with 75% showing an improvement in seizure control compared with 25% of children with normal educational functioning. Topiramate was withdrawn in 25 patients. The reasons for withdrawal included adverse effects in 20, lack of effect in three and worsening of seizures in two patients.

Adverse side effects were reported in 57% of the 51 patients. The majority of the side effects were related to behavioural and cognitive difficulties, with less-common side effects including anorexia, weight loss and headaches.

Key words: topiramate; children; adolescents; open study.

INTRODUCTION

Topiramate is a novel anticonvulsant drug with what appears to be a broad spectrum of activity. The drug was initially introduced as adjunctive therapy for refractory partial seizures in adults[1], but has subsequently been reported to be effective in a range of epilepsy syndromes and seizure types, including in children[2–9]. A number of these reports have included randomized controlled trials (RCTs)[4,5] which are primarily designed to satisfy regulatory requirements in order that the drug can be licensed. Unfortunately, RCTs provide little pragmatic information on how the drug can be used in everyday clinical practice. Thus far there are limited data on the open use of topiramate in children outside controlled trials[7,8].

The purpose of this retrospective review of all children treated with topiramate over a period of 3 years in a tertiary referral epilepsy centre is to describe the effectiveness and safety of the drug and to identify any specific practical difficulties with its use.

MATERIALS AND METHODS

Data were obtained from the computerized database of the pharmacy department at Alder Hey Children's Hospital. Topiramate was first prescribed in the hospital in June 1996 and data were collected up to March 1999, representing a period of 33 months. All prescriptions were initiated or recommended by the three paediatric neurologists who supervise seizure or neurology clinics within the hospital. Fifty-one patients were prescribed topiramate during this period.

Data were collected on seizure type, classification of epilepsy, epilepsy syndrome, presence or absence of learning difficulties, behavioural problems, the presence or absence of psychiatric illness prior to treatment with topiramate and treatment with other antiepileptic drugs.

Information was also collected on the age at which treatment was commenced, the starting dose, the duration over which the treatment was titrated, the maximum dose prescribed and the overall duration of treatment.

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Information was not collected on any haematological or biochemical data, including serum levels of topiramate or other antiepileptic drugs, primarily because such measurements are not usually undertaken in the routine clinical management of our patients with epilepsy.

The epilepsy syndromes were classified according to the International League Against Epilepsy classification.

Efficacy was based on seizure frequency with data obtained from seizure diaries completed by the child's parents and carers (and, where appropriate, teachers). In the absence of seizure diaries, efficacy was more crudely determined by whether the child and their usual carers considered that seizure frequency had improved.

The frequency of any hospital admissions because of increasing seizures, the development of adverse effects or episodes of convulsive and non-convulsive status epilepticus were also recorded.

Safety and tolerability of the drug were based on spontaneously reported side effects by the child or their carers.

Statistics were descriptive primarily because of the relatively small number and the heterogeneous nature of the study population.

Nineteen patients were reported to have had pre-existing behaviour problems including attention deficit hyperactivity disorder (ADHD), temper outbursts and 'mood swings'. None of these 19 patients had required formal psychiatric intervention and no patient was known to have suffered from any previous or concurrent psychiatric illness including depression or psychosis.

RESULTS

Study population

The characteristics of the 51 children are summarized in Table 1.

Thirty-one children suffered severe, 12 mild to moderate and eight no pre-existing learning difficulties. Twenty-three patients (45%) had cerebral palsy and 10 patients (20%) were fed via a percutaneous feeding gastrostomy tube.

Prior to the prescription of topiramate, 26 patients (51%) were experiencing at least daily seizures, 10 (19%) had a seizure frequency of at least one a week and the remaining 15 (29%) reported a range of seizure frequencies (the least being about one seizure every month).

At the time topiramate was introduced, 21 patients were receiving one, 25 patients two, and five patients three antiepileptic drugs. Thirty-two patients were receiving lamotrigine, 19 sodium valproate, 13 phenytoin, eight carbamazepine and the remaining 19 children were receiving other antiepileptic drugs including vigabatrin, a benzodiazepine (clobazam or clonazepam) and phenobarbitone.

Table 1: Demographic features of the 51 patients.

Sex distribution	Male/Female	32/19
Behavioural problems		19
Learning difficulties	None	8
	Mild/moderate	12
	Severe	31
Epilepsy diagnosis	Symptomatic generalized	30
	Idiopathic generalized	5
	Lennox–Gastaut syndrome	9
	Cryptogenic partial	4
	Symptomatic partial	3

Two patients were receiving methylphenidate for ADHD prior to the introduction of topiramate.

The mean duration of follow-up was 19 months (range 6–33) months.

The median age at which topiramate was introduced was 8.5 years (range 3.5–16 years).

For all children aged 12 years and over in this study, topiramate was introduced according to the data-sheet recommendation. Specific paediatric recommendations were introduced following a product licence for use as add-on therapy in children advising a maximum starting dose of 0.5 mg/kg/day and increasing every 2 weeks.

At the time that the majority of our younger patients were being treated with topiramate, there was no paediatric licence, and therefore no data-sheet recommendation for the use of the drug in children under 12 years of age. In these patients the drug was also introduced at a starting dose of 0.5 mg/kg/day. Although 46 patients, irrespective of age, had their dose increased every 2 weeks, achieving a target maintenance dose after 6–10 weeks, two patients had a more rapid escalation over a 3-week period and three had a slower escalation of the dose over 6 months.

The mean maintenance daily dose was 169 mg, range 25–500 mg; the one patient who received 500 mg/day weighed 75 kg on her last clinic visit. The mean maintenance dose, based on body weight, was 6.7 mg/kg/day (this information was only available on 36 of the 51 patients because of missing bodyweight data on the remaining 15 patients).

The mean duration of treatment was 10.8 months (range 3 weeks–32 months). Twenty children received topiramate for more than 1 year and nine children for more than 2 years. In 25 children (49%) topiramate was withdrawn within 6 months of introduction, 20 of whom developed adverse side effects including behaviour and cognitive difficulties (17 children) and anorexia and weight loss (three children). In two more

Table 2: Reported adverse effects[a].

Adverse effect	Number of children	%
Behavioural/cognitive:		
Agitation/irritability	7	13
Depression	7	13
Lethargy/no energy	5	10
Visual hallucinations	1	3
Neurological:		
Anorexia/weight loss	3	6
Ataxia	3	6
Aphasia	1	2
Other:		
Diarrhoea	3	6
Headaches	3	6

[a] Some patients experienced more than one adverse effect.

children withdrawal was due to the combination of lack of efficacy and adverse side effects, while the remaining three children stopped taking topiramate because of lack of efficacy.

Twenty-six children (51%) were still receiving topiramate at the time of their last clinic review. Twenty-two of the 51 patients (43%) reported initial improvement in seizure control and of these 22 patients, 15 (29% of the 51 patients) showed a sustained improvement over a period of 4–6 months. In two patients the drug had to be discontinued because of intolerable side effects despite a marked reduction in seizure frequency including seizure freedom in one of these two patients.

Of the 15 patients who showed a sustained response, five (33%) had symptomatic generalized epilepsy, three (20%) had Lennox–Gastaut syndrome and three (20%) had complex partial epilepsy with secondary generalization.

Four of the 51 patients (8%) became seizure free, two with a cryptogenic partial epilepsy, one with a symptomatic generalized epilepsy (secondary to congenital toxoplasmosis) and one with a cryptogenic generalized epilepsy characterized by drop attacks. It was not possible to analyse efficacy for different seizure types (i.e. myoclonic, tonic, typical and atypical absences) because the limited documentation militated against this specific analysis.

Adverse events were reported by the child, or more commonly the child's carers (usually the parents). Twenty-nine children (57%) reported a total of 39 adverse effects following the prescription of topiramate (Table 2). Twenty-nine of these adverse effects (74%) were behavioural, cognitive or neurological in nature. Three children aged 9, 13 and 14 years, developed episodes of unexplained and at times inconsolable crying and the 14-year-old boy expressed suicidal thoughts and two episodes of self harm; symptoms resolved in all three children on discontinuation of topiramate. In most children the behavioural changes were severe and led to withdrawal of the drug in 17 children, in spite of an initial reduction in the daily dose of topiramate.

Anorexia and weight loss developed in three children, which persisted after a 25–50% reduction in the dose of topiramate and eventually led to drug withdrawal.

No patient was known to have experienced any symptoms suggesting the development of renal calculi, throughout the period of evaluation.

DISCUSSION

This retrospective audit of a group of children with chronic epilepsy has demonstrated first that topiramate appears to be effective in controlling a range of seizure types in a number of children, and secondly that the drug may be associated with significant behavioural and cognitive side effects necessitating drug withdrawal.

It must be emphasized that our study population was heterogeneous in terms of seizure type, epilepsy syndrome, aetiology and cognitive function and in addition, was comprised of children with previously intractable epilepsy receiving a mean of 1.68 additional antiepileptic drugs. Most had received the other 'new' antiepileptic drugs, including lamotrigine, vigabatrin and gabapentin, and, therefore, represented a very refractory epilepsy population.

Despite the refractory nature of our patients, four of our 51 patients (8%) became seizure free for periods of between 6 and 15 months at the time of their last review. In three of these children, their other antiepileptic drugs (AEDs) could be withdrawn leaving them seizure free on topiramate monotherapy. In addition, almost one third showed a significant and sustained improvement in seizure control and in most of these patients the reduction in seizure frequency was between 50 and 75%. These findings are similar to reported results of an open study from a tertiary epilepsy centre where 8% of 39 children with refractory epilepsy also became seizure free and an additional 21% showed a greater than 50% reduction in seizure frequency[7]. An additional open study reported a greater than 50% reduction in partial seizures in 28 of 49 (57%) children after 6 months treatment with topiramate[8]; in contrast, no patient with a generalized epilepsy syndrome apparently achieved a 50% reduction in seizure frequency[8]. However, an earlier placebo-controlled study in 96 children with refractory partial seizures reported a responder rate (i.e. a $>50\%$ reduction in seizure frequency) in 39%, with two of the 41 topiramate-treated children (5%) becoming seizure free[4]. A controlled study in 98 patients with Lennox–Gastaut syndrome demonstrated a greater than 50% reduction in major (i.e. drop attacks and tonic–clonic) seizures in 15 of the 46 (33%) topiramate-treated patients[5]. In addition, in five of these 46 children, drop

attacks completely ceased in the final 8 weeks of the double-blind treatment phase.

The controlled trial data[4,5], together with the findings of Uldall and Buchholt[7] and the present study, suggest that topiramate does have a relatively broad spectrum of action against both partial and generalized epilepsies. However, there is some evidence that topiramate may be more effective in partial rather than generalized epilepsies (irrespective of whether idiopathic or symptomatic origin[3,8]), although this could not be confirmed in the present report because of the small number of children who were considered to have a partial epilepsy. As yet, it is also not possible to provide any definitive information on the response of different seizure types to topiramate because of limited data in both the open and controlled studies.

Although our study population is relatively small, it did appear that those children with mild or moderate learning difficulties showed a greater reduction in seizures compared with those with either severe or no learning difficulties. There is little or no evidence to support or refute this observation because most of the published paediatric data have involved children with chronic and refractory epilepsy, usually in association with moderate or severe learning difficulties, and not in children of normal intellectual ability.

Finally, limited data again precluded the identification of whether topiramate used in combination with any other specific AED proved particularly beneficial in improving seizure control. An earlier open study has suggested that the combination of topiramate with gabapentin, carbamazepine or felbamate may be particularly effective[8].

Twenty-nine of our patients or their carers (57%) spontaneously reported adverse side effects, the majority of which (74%) were either behavioural or cognitive in nature and included depression, marked irritability or aggression, psychosis and aphasia. A number of parents reported that their children appeared to always be tired or had difficulties with short-term memory; similar comments were expressed by the childrens' teachers, including those children attending special schools. Anorexia and weight loss were uncommon but severe, and in one child led to the parents requesting discontinuation of the drug despite the child being seizure free.

The frequency of adverse side effects in this study is almost identical to two earlier open paediatric studies which reported an incidence of 54% in 39[7] children, and at least 53% of 49 children[8]. However, the type of adverse effects reported was different between the two studies. In the study by Moreland *et al.*[8], behavioural and cognitive side-effects predominated with 53% of patients experiencing 'decreased cognition, decreased speech, decreased energy or worsened behaviour'. Twenty-eight patients in this study also experienced a reduction in appetite. After 6 months of treatment, only 34 of the original 49 patients were available for review; the authors did not stipulate how many of the remaining 15 patients were no longer taking topiramate because of lack of efficacy or adverse effects or both. In contrast to this study, the predominant side effect in the report by Uldall and Buchholt[7] was weight loss (39%) with behavioural and cognitive difficulties being found in only 21% (sedation/slow thinking) and ataxia/clumsiness in a further 8%. In this study by Uldall and Buchholt[7], the degree of weight loss was not specified but was reported to be not severe and subsided, except in two children who required gastric tube feeding for up to 12 months; no patient withdrew from topiramate because of weight loss or persisting anorexia.

Weight loss and sedation were the most commonly reported adverse side effects in the two controlled studies in partial epilepsy[4] and Lennox–Gastaut syndrome[5], although disturbances of mood, aggressive reactions, 'nervousness' and other behavioural problems were also recorded in between 10 and 21% of patients[4,5]. Perhaps surprisingly, no patient in these two controlled studies withdrew due to any adverse events.

One explanation for the lower incidence of anorexia and weight loss in our study could be due to the fact that 20% of our patients were fed exclusively by a feeding gastrostomy tube and therefore anorexia would not have been identified. Although the majority of the patients reported by Uldall and Buchholt[7] had moderate or severe learning difficulties, there was no information on how many, if any of these children also were fed through gastrostomies.

In adults, the most frequently reported adverse effects include behavioural and cognitive difficulties with an incidence of almost 50% in one retrospective review of 174 patients[3]. In this study 90 of the 174 patients had stopped taking the drug at the end of 12 months, many due to adverse effects, and usually within the first 3–4 months of taking topiramate. Finally there has also been a report of an acute psychosis which resolved on discontinuation of the drug[10].

Finally, most of our patients who developed adverse effects failed to improve despite reductions in their dose of topiramate (often as much as a 50–60% reduction) and eventually had to discontinue the drug.

In conclusion, it is clear from both this and earlier controlled and open studies that topiramate is a potent antiepileptic drug which appears to have a broad spectrum of action in the cryptogenic/symptomatic partial and generalized epilepsies. Its role in the treatment of the idiopathic generalized epilepsy syndromes and primary generalized seizures (i.e. tonic–clonic, typical absence and myoclonic) is as yet unclear[2]. However, the use of topiramate may also be complicated by a number of adverse side effects, particularly affecting

behaviour, cognitive function and appetite, which in many patients, may necessitate premature discontinuation of the drug, in spite of excellent seizure control. These predominantly neuropsychiatric adverse side-effects obviously justify caution in using topiramate in patients with pre-existing learning difficulties or behaviour problems (or both)[11]. However, it is also important that the use of this drug is carefully considered on a risk:benefit basis before prescribing it to children of normal intellectual ability. Although these adverse effects may potentially be avoided or minimized by a slow titration of the drug (e.g. a starting dose of 0.5 mg/kg/day increased every 2 weeks up to an initial target maintenance dose of 4–5 mg/kg/day achieved over a minimum of 8 weeks), it seems that there will remain a number of paediatric patients who are intolerant of the drug. Finally, as in the treatment of the majority of children with epilepsy, specific care should be taken when using topiramate with another AED; future data may or may not identify a particularly effective (or problematic) combination of topiramate with another AED.

Finally, although the introduction of topiramate has undoubtedly offered clinicians an additional treatment option for improving their patients' seizure control, the resulting expansion in available options has created a therapeutic dilemma—namely at which stage topiramate should be prescribed. This dilemma may be resolved by future comparative studies, including the NHS R and D-funded Standard and New Antiepileptic Drugs ('SANAD') study.[†]

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[†] Further information on the 'SANAD' study may be obtained from: The SANAD Office, University Department of Neurological Science, The Walton Centre for Neurology and Neurosurgery, Liverpool, L9 7LJ. Telephone: 0151 529 5464, Fax: 0151 529 5466.